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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/001,221 | 10/30/2001 | Thomas J. Schall | 10709-014 | 2004 |

7590 06/03/2004

Scott Ausenhus, ESQ.
Townsend Townsend & Crew
1200 Seventeenth Street
Suite 27000
Dever, CO 80202

| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | |

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/001,221 | SCHALL ET AL. | |
| | Examiner | Art Unit | |
| | Karen A Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *69-88* is/are pending in the application.

4a) Of the above claim(s) *76-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *69-75, 79-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Acknowledgement is made of applicant election without traverse of Group II, drawn to compositions comprising at least one chemokine and at least one antigen. Acknowledgement is also made of applicants election of the species of mC10 and vMCK-2 as chemokines and tumor antigens as antigen.

Claims 1-68 have been canceled. Claims 69-88 have been added. Claims 76-78, drawn to non-elected species, are withdrawn from consideration, Claims 69-75 and 79-88 are examined on the merits.

Acknowledgment is made of applicant claims to an earlier effective filing date via 09/834,814, filed April 20, 2001 and 60/198,839. filed April 21, 2000. Upon review of the '839 application, it is noted that no support was found for MCK-2 or vMCK-2 as part of the instant invention. Accordingly, the instant claims are given the effective priority date of the '814 application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 69-72, 74, 75, 79-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al (Advances in Cancer Research, 1992, Vol. 59, pp. 245-322) in view of Bystryn (WO 98/33520) and Mohamadzadeh et al (Archives of Dermatological Research, 1997, Vol. 289, pp. 435-439) and Orlofsky et al (Cytokine, March 2000, Vol. 12, pp. 220-228)

Kedar et al teach that preclinical and clinical studies indicate that antigenicity of a tumor and the capacity to mobilize a T-cell response are required for successful immunotherapy(page 254, lines 3-5). Kedar et al teach that infiltrating macrophage, neutrophils and eosinophils are present in regressing tumors indicating that said infiltrating cells are mobilized by lymphokines released from the antigen-specific T-cells. (page 255. lines 5-11). Kedar et al teach that said cells are contributing to the therapeutic effect (page 256, lines 1-2). Kedar et al teach stealth liposomes which can evade the reticuloendothelial system thereby achieving a prolonged circulation time and enhanced accumulation in tumors in various body compartments (page 266, lines 10-20). It is noted that said stealth liposomes are taught by Kedar et al to be smaller than 0.1 um, and thus fulfill the specific embodiment of claim 80 drawn to a microsphere. Kedar et al teach that administration of biological modifiers such as cytokines by encapsulation in liposomes bypasses the need for continuous infusion or frequent bolus administrations to counteract the short plasma half-lives of cytokines or other biological response modifiers (page 265, lines 1-6 under the heading "New Methods for Delivery of cytokines and Other Biological Response Modifiers"). Kedar also teach that tumor antigens encapsulated in liposomes can improve the immunogenicity of said tumor antigen in human patients and that administration of the tumor antigen together with cytokines and improved adjuvants demonstrate increased anti-tumor efficacy in experimental animals (page 287, lines 16-35 under the heading "Active Specific Immunotherapy"). Kedar et al teach that treatment with combinations of cytokines differing in their mode of action, each at subtoxic doses may improve the therapeutic index (page 260, lines 5-7, under the heading "Cytokine Combinations"). Kedar et al do not specifically teach C10 as a biological response modifier, or an encapsulated liposome comprising a chemokine, adjuvant and a tumor antigen.

Bystryn (WO 98/33520) teaches pH sensitive liposomes (page 2, line 21 to page 3, line 18) and encapsulated vaccine containing immunomodulators (page 5, lines 3-7 and page 6, line 1

to page 7, line 2). Bystryn teaches oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical administration of the vaccines (page 30, lines 4-12). Bystryn teaches that pH sensitive liposomes are taken up by antigen-presenting cells (page 3, lines 5-8) .

Mohamadzadeh et al (Archives of Dermatological Research, 1997, Vol. 289, pp. 435-439) teach that both dendritic and Langerhan's cells are sources of the C10 chemokine for the recruitment of T cells and cytokines involved in initiation of inflammatory events (page 438, second column, lines 28-32) in addition to the processing and presentation of protein antigens and the induction of primary T cell response

Orlofsky et al (Cytokine, March 2000, Vol. 12, pp. 220-228) teach that the murine chemokine C10 modulated immune reactions of the Th2 type (page 225, second column, lines 9-11). Orlofsky et al teach that subsequent development of a Th2 response is ineffective at suppressing C10 expression (page 225, second column, lines 14-17). Orlofsky et al conclude that the decisive period for C10 regulation would thus be before C10 expression is induced and therefore during the generation of early inflammatory signals (page 225, second column, lines 17-21). Orlofsky et al teach that C10 is chemotactic for macrophages and T and B lymphocytes and that C10 acts to maintain modes of cellular interactivity previously initiated by the more transient chemokines such as MIP-1 alpha, or that C10 specifically attracts one or more T cell subsets.

It would have been prima facie obvious at the time the claimed invention was made to use C10 for the immunomodulator in the stealth liposomes taught by Kedar et al. It would have been further obvious to combine C10 with a tumor antigen, an additional chemokine and an adjuvant in said liposome for a prolonged circulation time in a patient and to administer said liposomes by oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical routes. One of skill in the art would have been motivated to do so by the teachings of Kedar et al on the accumulation of said stealth liposomes at the tumor site; and the teachings of Orlofsky et al on the maintenance of the Th2 response by C10 and the teachings of both Orlofsky et al and Mohamadzadeh et al on the recruitment by C10 of T cells and cytokines involved in the inflammatory response. One of skill in the art would also have been motivated to combine the liposome encapsulated C10 with the tumor antigen because Kedar et al teaches that encapsulation of tumor antigens within liposomes can improve the immunogenicity of said

tumor antigen. One of skill in the art would have been motivated to combine the MCK-2 chemokine with an additional chemokine in order to exert an additive or synergistic effect. It is noted that the encapsulation of both the C10 chemokine and the tumor antigen within the liposome fulfill the specific embodiment of claim 75 drawn to the composition wherein the chemokine an the antigen are linked because occupying the same interior space of a liposome is a linkage between the chemokine and the tumor antigen. One of skill in the art would be motivated to further encapsulate the adjuvant by the teachings of Bystryn et al. Furthermore, one of skill in the art would be motivated to prepare sterile preparations of the liposome encapsulated pharmaceuticals in order to preserve the shelf life of said compositions and in order to prevent contamination with a pathogenic agent.

Claims 69-73, 75, 79-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al (Advances in Cancer Research, 1992, Vol. 59, pp. 245-322) in view of Bystryn (WO 98/33520) and Saederup et al (PNAS, Sep 1999, vol. 96, pp. 10881-10886).

Kedar et al teach that preclinical and clinical studies indicate that antigenicity of a tumor and the capacity to mobilize a T-cell response are required for successful immunotherapy(page 254, lines 3-5). Kedar et al teach that infiltrating macrophage, neutrophils and eosinophils are present in regressing tumors indicating that said infiltrating cells are mobilized by lymphokines released from the antigen-specific T-cells. (page 255. lines 5-11). It is noted that said stealth liposomes are taught by Kedar et al to be smaller than 0.1 um, and thus fulfill the specific embodiment of claim 80 drawn to a microsphere. Kedar et al teach that said cells are contributing to the therapeutic effect (page 256, lines 1-2). Kedar et al teach stealth liposomes which can evade the reticuloendothelial system thereby achieving a prolonged circulation time and enhanced accumulation in tumors in various body compartments (page 266, lines 10-20). Kedar et al teach that administration of biological modifiers such as cytokines by encapsulation in liposomes bypasses the need for continuous infusion or frequent bolus administrations to counteract the short plasma half-lives of cytokines or other biological response modifiers (page 265, lines 1-6 under the heading "New Methods for Delivery of cytokines and Other Biological Response Modifiers"). Kedar also teach that tumor antigens encapsulated in liposomes can

improve the immunogenicity of said tumor antigen in human patients and that administration of the tumor antigen together with cytokines and improved adjuvants demonstrate increased anti-tumor efficacy in experimental animals (page 287, lines 16-35 under the heading "Active Specific Immunotherapy"). Kedar et al teach that treatment with combinations of cytokines differing in their mode of action, each at subtoxic doses may improve the therapeutic index (page 260, lines 5-7, under the heading "Cytokine Combinations"). Kedar et al do not specifically teach C10 as a biological response modifier, or an encapsulated liposome comprising a chemokine, adjuvant and a tumor antigen.

Bystryn (WO 98/33520) teaches pH sensitive liposomes (page 2, line 21 to page 3, line 18) and encapsulated vaccine containing immunomodulators (page 5, lines 3-7 and page 6, line 1 to page 7, line 2). Bystryn teaches oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical administration of the vaccines (page 30, lines 4-12). Bystryn teaches that pH sensitive liposomes are taken up by antigen-presenting cells (page 3, lines 5-8) .

Saederup et al (PNAS, Sep 1999, vol. 96, pp. 10881-10886) teach that Mck-1/Mck-2 are responsible for promoting host leukocyte chemotaxis and may be responsible for attracting monocytes and macrophage as well (abstract, lines 15-18). Saederup et al teach that both MCK-1 and MCK-2 have the same chemokine domain but that MCK-2 contains an additional 199 amino acid sequence as a novel carboxyl terminus resulting form alternative RNA splicing (page 10881, second column, lines 8-13). Saederup et al teach that the observed data indicate that MCK-1 can recruit and activate monocytes or macrophages (page 10885, first column, lines 7-12). Saederup et al teach that MCK-1/MCK-2 mutant cannot sustain an inflammation relative to non-mutated MCK-1/MCK-2 consistent with the role of maintaining monocyte migration (page 10886, lines 36-40).

It would have been prima facie obvious at the time the claimed invention was made to use C10 for the immunomodulator in the stealth liposomes taught by Kedar et al. It would have been further obvious to combine MCK-2 with a tumor antigen, an additional chemokine, and an adjuvant in said liposome for a prolonged circulation time in a patient and to administer said liposomes by oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical routes. One of skill in the art would have been motivated to do so by the teachings of Kedar et al on the accumulation of said stealth liposomes at the tumor site and the benefits of administering

combinations of cytokines; and the teachings of Kedar et al on the therapeutic effect associated with recruitment of macrophage and monocytes to the tumor site and the teachings of Saederup et al on the recruitment of macrophage and monocytes by MCK-1/MCK-2. One of skill in the art would conclude that MCK-1 and MCK-2 can be used interchangeably because both MCK-1 and 2 contain the same chemokine domain and because mutation of either MCK-1 or MCK-2 can abrogate inflammation relative to the wild type. One of skill in the art would also have been motivated to combine the liposome encapsulated MCK-2 with the tumor antigen because Kedar et al teaches that encapsulation of tumor antigens within liposomes can improve the immunogenicity of said tumor antigen. One of skill in the art would have been motivated to combine the MCK-2 chemokine with an additional chemokine in order to exert an additive or synergistic effect. It is noted that the encapsulation of both the MCK-2 chemokine and the tumor antigen within the liposome fulfills the specific embodiment of claim 75 drawn to the composition wherein the chemokine an the antigen are linked because occupying the same interior space of a liposome is a linkage between the chemokine and the tumor antigen. One of skill in the art would be motivated to further encapsulate the adjuvant by the teachings of Bystryn n et al. Furthermore, one of skill in the art would be motivated to prepare sterile preparations of the liposome encapsulated pharmaceuticals in order to preserve the shelf life of said compositions and in order to prevent contamination with a pathogenic agent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella
06/01/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER